

CLAIMS

What is claimed is:

1. An isolated antibody or an antigen-binding fragment thereof, comprising:
 - (a) a heavy chain variable domain (VH) comprising:
 - i. complementarity a heavy chain determining region 1 (CDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:27-39;
 - ii. a heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:40-52; and
 - iii. a heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:53-65, respectively; and
 - (b) a light chain variable domain (VL) comprising:
 - i. a light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:66-78;
 - ii. a light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:79-91; and
 - iii. a light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:92-104, respectively;

wherein the antibody or antigen-binding fragment thereof is capable of specifically binding to a TIGIT, preferably a human TIGIT.

~~2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein:~~

- ~~(1) the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:27, 40, and 53, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:66, 79, and 92, respectively;~~
- ~~(2) the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:28, 41, and 54, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:67, 80, and 93, respectively;~~
- ~~(3) the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:29, 42, and 55, respectively, and the VL comprises the~~

light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:68, 81, and 94, respectively;

- (4) the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:30, 43, and 56, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:69, 82, and 95, respectively;
- (5) the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:31, 44, and 57, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:70, 83, and 96, respectively;
- (6) the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:32, 45, and 58, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:71, 84, and 97, respectively;
- (7) the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:33, 46, and 59, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:72, 85, and 98, respectively;
- (8) the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:34, 47, and 60, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:73, 86, and 99, respectively;
- (9) the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:35, 48, and 61, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:74, 87, and 100, respectively;
- (10) the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:36, 49, and 62, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:75, 88, and 101, respectively;

- (11) ~~the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:37, 50, and 63, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:76, 89, and 102, respectively;~~
- (12) ~~the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:38, 51, and 64, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:77, 90, and 103, respectively; or~~
- (13) ~~the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:39, 52, and 65, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:78, 91, and 104, respectively.~~
3. ~~The isolated antibody or antigen binding fragment thereof of claim 2, wherein the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs: 38, 51, and 64, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:77, 90, and 103, respectively.~~
4. ~~The isolated antibody or antigen binding fragment thereof of claim 2, wherein the VH comprises the heavy chain CDR1, CDR2, and CDR3 sequences having the amino acid sequences of SEQ ID NOs:39, 52, and 65, respectively, and the VL comprises the light chain CDR1, CDR2, and CDR3 having the amino acid sequences of SEQ ID NOs:78, 91, and 104.~~
5. ~~The isolated antibody or antigen binding fragment thereof of any one of claims 1-4, wherein the VH comprises an amino acid sequence that is at least 90% identical to a sequence selected from the group consisting of SEQ ID NOs:1-13, and the VL comprises an amino acid sequence that is at least 90% identical to a sequence selected from the group consisting of SEQ ID NOs:14-26, respectively.~~
6. ~~The isolated antibody or antigen binding fragment thereof of claim 5, wherein the VH comprises the amino acid sequence selected from the group consisting of SEQ ID NOs:1-13, or a variant thereof comprising up to about 3 amino acid substitutions in the VH; and the VL comprises the amino acid sequence selected from the group consisting of SEQ ID NOs:14-26, or a variant thereof comprising up to about 3 amino acid substitutions in the VL.~~

7. — The isolated antibody or antigen binding fragment thereof of claim 5 or 6, wherein:
- (1) the VH comprises an amino acid sequence of SEQ ID NO:1, and the VL comprises an amino acid sequence of SEQ ID NO:14;
 - (2) the VH comprises an amino acid sequence of SEQ ID NO:2, and the VL comprises an amino acid sequence of SEQ ID NO:15;
 - (3) the VH comprises an amino acid sequence of SEQ ID NO:3, and the VL comprises an amino acid sequence of SEQ ID NO:16;
 - (4) the VH comprises an amino acid sequence of SEQ ID NO:4, and the VL comprises an amino acid sequence of SEQ ID NO:17;
 - (5) the VH comprises an amino acid sequence of SEQ ID NO:5, and the VL comprises an amino acid sequence of SEQ ID NO:18;
 - (6) the VH comprises an amino acid sequence of SEQ ID NO:6, and the VL comprises an amino acid sequence of SEQ ID NO:19;
 - (7) the VH comprises an amino acid sequence of SEQ ID NO:7, and the VL comprises an amino acid sequence of SEQ ID NO:20;
 - (8) the VH comprises an amino acid sequence of SEQ ID NO:8, and the VL comprises an amino acid sequence of SEQ ID NO:21;
 - (9) the VH comprises an amino acid sequence of SEQ ID NO:9, and the VL comprises an amino acid sequence of SEQ ID NO:22;
 - (10) the VH comprises an amino acid sequence of SEQ ID NO:10, and the VL comprises an amino acid sequence of SEQ ID NO:23;
 - (11) the VH comprises an amino acid sequence of SEQ ID NO:11, and the VL comprises an amino acid sequence of SEQ ID NO:24;
 - (12) the VH comprises an amino acid sequence of SEQ ID NO:12, and the VL comprises an amino acid sequence of SEQ ID NO:25; or
 - (13) the VH comprises an amino acid sequence of SEQ ID NO:13, and the VL comprises an amino acid sequence of SEQ ID NO:26.
8. — The isolated antibody or antigen binding fragment thereof of claim 7, wherein the VH comprises the amino acid sequence of SEQ ID NO:12, and the VL comprises the amino acid sequence of SEQ ID NO:25.

9. — The isolated antibody or antigen binding fragment thereof of claim 7, wherein the VH comprises the amino acid sequence of SEQ ID NO:13, and the VL comprises the amino acid sequence of SEQ ID NO:26.
10. — The isolated antibody or antigen binding fragment thereof of any one of claims 1-9, wherein the VH is fused to a heavy chain constant region of an immunoglobulin.
11. — The isolated antibody or antigen binding fragment thereof of any one of claims 1-10, wherein the VL is fused to a light chain constant region (CL) of an immunoglobulin.
12. — The isolated antibody or antigen binding fragment thereof of any one of claims 1-11, wherein the K_D of the binding between the antibody or antigen binding fragment thereof and the TIGIT is 10^{-7} M to about 10^{-12} M, preferably about 10^{-8} M to about 10^{-12} M, more preferably about 10^{-9} M to about 10^{-12} M.
13. — The isolated antibody or antigen binding fragment thereof of any one of claims 1-12, being rodent, chimeric, human, partially humanized, or fully humanized.
14. — The isolated antibody or antigen binding fragment thereof of claim 13, being humanized.
15. — The isolated antibody or antigen binding fragment thereof of claim 14, wherein the VH comprises the amino acid sequence selected from the group consisting of SEQ ID NOs:105-112, and the VL comprises the amino acid sequence selected from the group consisting of SEQ ID NOs:113-118.
16. — The isolated antibody or antigen binding fragment thereof of any one of claims 1-15, further comprising a second antibody moiety, wherein the second antibody moiety is capable of specifically binding to a second antigen.
17. — The isolated antibody or antigen binding fragment thereof of claim 16, wherein the second antibody moiety is a Fab, a Fab', a (Fab')₂, an Fv, a single chain Fv (scFv), an scFv-scFv, a minibody, a diabody, an sdAb, or an antibody mimetic.
18. — The isolated antibody or antigen binding fragment thereof of claim 17, wherein the second antibody moiety is an sdAb.
19. — The isolated antibody or antigen binding fragment thereof of any one of claims 16-18, wherein the second antibody moiety is capable of specifically binding to CTLA-4, preferably, the second antibody moiety is an sdAb capable of specifically binding to CTLA-4.

20.— ~~The isolated antibody or antigen-binding fragment thereof of any one of claims 16-18, wherein the second antibody moiety is capable of specifically binding to PD-L1, preferably, the second antibody moiety is an sdAb capable of specifically binding to PD-L1.~~

21.— ~~The isolated antibody or antigen-binding fragment thereof of any one of claims 16-18, wherein the second antibody moiety is capable of specifically binding to TIM-3, preferably, the second antibody moiety is an sdAb capable of specifically binding to TIM-3.~~

22.— ~~The isolated antibody or antigen-binding fragment thereof of any one of claims 16-18, wherein the second antibody moiety is capable of specifically binding to LAG-3, preferably, the second antibody moiety is an sdAb capable of specifically binding to LAG-3.~~

23.— ~~The isolated antibody or antigen-binding fragment thereof of any one of claims 19-22, wherein the amino-terminus of the heavy chain or light chain of a full-length IgG capable of specifically recognizing TIGIT is fused, optionally via a peptide linker, to the carboxyl terminus of the sdAb capable of specifically binding to CTLA-4, PD-L1, TIM-3, or LAG-3.~~

24.— ~~The isolated antibody or antigen-binding fragment thereof of any one of claims 19-22, wherein the carboxyl-terminus of the heavy chain or light chain or a full-length IgG capable of specifically recognizing TIGIT is fused, optionally via a peptide linker, to the amino-terminus of the sdAb capable of specifically binding to CTLA-4, PD-L1, TIM-3, or LAG-3.~~

25.— ~~The isolated antibody or antigen-binding fragment thereof of claim 23 or 24, wherein the full-length IgG capable of specifically recognizing TIGIT is fused to the sdAb capable of specifically binding to CTLA-4, PD-L1, TIM-3, or LAG-3 via a peptide linker having the amino acid sequence of one of SEQ ID NOs:119-121.~~

26.— ~~A second isolated antibody or antigen-binding fragment thereof capable of specifically binding to TIGIT competitively with the isolated antibody or antigen-binding fragment thereof of any one of claims 1-25.~~

27.— ~~A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1-25 or the second isolated antibody or antigen-binding fragment thereof of claim 26, and a pharmaceutically acceptable carrier.~~

28.— ~~The isolated antibody or antigen-binding fragment thereof of any one of claims 1-25, the second isolated antibody or antigen-binding fragment thereof of claim 26 or the pharmaceutical composition of claim 27, for use in treating a TIGIT-related disease in a subject in need thereof.~~

29. ~~The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 28, wherein the TIGIT-related disease is a cancer.~~
30. ~~The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 29, wherein the cancer is a solid tumor.~~
31. ~~The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 29, wherein the cancer is a colon cancer.~~
32. ~~The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 28-31 in combination with an additional cancer therapy.~~
33. ~~The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 32, wherein the additional cancer therapy is a surgery, radiation, chemotherapy, immunotherapy, hormone therapy, or a combination thereof.~~
34. ~~The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of claim 28, wherein the TIGIT-related disease is a pathogenic infection.~~
35. ~~The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 28-34, wherein the isolated antibody or antigen-binding fragment or pharmaceutical composition is for systemic or local administration.~~
36. ~~The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 28-34, wherein the isolated antibody or antigen-binding fragment or pharmaceutical composition is for intravenous administration.~~
37. ~~The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition for use of any one of claims 28-34, wherein the isolated antibody or antigen-binding fragment or pharmaceutical composition is for intratumoral administration.~~
38. The isolated antibody or antigen-binding fragment thereof or pharmaceutical composition comprising the isolated antibody or antigen-binding fragment thereof or a second isolated antibody or antigen-binding fragment thereof capable of specifically binding to TIGIT competitively with the isolated antibody or antigen-binding fragment thereof, and a pharmaceutically acceptable carrier for use in treating a TIGIT related disease in a subject in need thereof of any one of claims 28-37, wherein the subject is human.